UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF GEORGIA
ATLANTA DIVISION

MIMEDX GROUP, INC., Plaintiff, v. U.S. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	Case No. 1:24-cv-01287-SEG

DEFENDANTS' COMBINED OPPOSITION TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND CROSS-MOTION FOR SUMMARY JUDGMENT

OF COUNSEL:

SAMUEL R. BAGENSTOS
General Counsel
U.S. Department of Health and Human Services

WENDY VICENTE
Deputy Chief Counsel, Litigation

ELIZABETH NORFORD
Associate Chief Counsel
Office of the Chief Counsel
U.S. Food and Drug Administration
10903 New Hampshire Ave.
White Oak 31
Silver Spring, MD 20993-0002

BRIAN M. BOYNTON
Principal Deputy Assistant Attorney General

BURDEN H. WALKER
Acting Deputy Assistant Attorney General

AMANDA N. LISKAMM
Director

LISA K. HSIAO
Senior Deputy Director, Civil Litigation

HILARY K. PERKINS
Assistant Director

NOAH T. KATZEN
Trial Attorney
Consumer Protection Branch
Civil Division

U.S. Department of Justice
P.O. Box 386
Washington, DC 20044-0386
(202) 305-2428
(202) 514-8742 (fax)
Noah.T.Katzen@usdoj.gov

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INTRODUCTION

MiMedx brought this suit because it wants its product Axiofill to be regulated under a more limited form of regulatory oversight that does not require premarket review. It argues that the U.S. Food and Drug Administration (FDA) incorrectly applied the regulations governing how Axiofill is classified and that FDA's decision was inconsistent with its actions in other cases. But FDA correctly applied the relevant regulations here, consistent with the agency's well-settled interpretation of its regulations as detailed in agency guidance and with the agency's application of its regulations to other products. Thus, FDA's decision was reasonable and complied with the Administrative Procedure Act.

Axiofill is in a category of products known as human cells, tissues, or cellular or tissue-based products (HCT/Ps), which are "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d). FDA employs a "tiered, risk-based approach to regulating HCT/P's" in which "the regulation of different types of [HCT/Ps] will be commensurate with the public health risks presented." 66 Fed. Reg. 5447, 5447, 5449 (Jan. 19, 2001); *see* 42 U.S.C. § 264(a). Although FDA is authorized to apply standard premarket review requirements to these products, those HCT/Ps that meet certain risk-based criteria are regulated solely under Section 361 of the Public

Health Service Act (PHSA), which authorizes regulation to prevent the spread of communicable diseases, and the regulations in 21 C.F.R. Part 1271. 42 U.S.C. § 264(a). Such products are referred to as "361-only" HCT/Ps and do not require premarket review. By contrast, products that do not meet the risk-based criteria to be regulated as 361-only HCT/Ps do not qualify for the limited form of regulatory oversight and are regulated as a drug, device, and/or biological product, which requires premarket review. AR674–75.

One of the risk-based criteria for a 361-only HCT/P is that it must be "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). That requires "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1).

Axiofill is a powder intended to help treat wounded skin by replacing or supplementing damaged or inadequate tissue. Per MiMedx, "Axiofill is made from human placental disc, including but not limited to, the chorionic plate." AR241. It comprises a particulate placental disc extracellular matrix (ECM) preparation. Axiofill is manufactured by subjecting the isolated human placental disc to a series of processing steps, including cutting, rinsing in water, chopping, separating the tissue from the liquid, rinsing with a decellularization agent, freeze drying, grinding, and sieving.

FDA found that Axiofill is more than minimally manipulated because the processing "alters" the original relevant characteristics of the placental disc relating to its role as "a selective barrier that provides a transport function between different circulatory systems (e.g., the fetal and maternal circulatory systems)." AR259 & n.6 (citing "[t]he relevant scientific literature" describing this utility); AR262. Thus, FDA reasonably determined that Axiofill does not qualify as a 361-only HCT/P and that it should instead be regulated as a biological product.

MiMedx's challenges to FDA's decision are unavailing. Contrary to MiMedx's argument, FDA properly applied the minimal manipulation definition to the placental disc—the tissue from which MiMedx identifies Axiofill as being processed—rather than to Axiofill itself, which consists of an ECM preparation. The minimal manipulation definition refers to the "original relevant characteristics of the tissue," which are characteristics of the tissue in the donor. And while the placental disc exists in the donor, Axiofill (or the ECM preparation that comprises Axiofill) does not. Moreover, focusing on the placental disc rather than Axiofill is consistent with FDA's risk-based framework because it captures the full effect of processing on the tissue.

FDA also properly analyzed the original relevant characteristics of the tissue by looking at how the tissue behaves in the donor, not in the recipient. The

tissue's function in the donor indicates how the tissue could be useful to provide "reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1). MiMedx argues that the analysis should focus on the characteristics of the HCT/P that make it useful in the recipient, but the minimal manipulation criterion does not assess the HCT/P's actual effectiveness in the recipient. Moreover, the criteria for 361-only HCT/Ps are designed to identify HCT/Ps whose risks are adequately addressed under limited regulatory oversight and *without* premarket review for safety and effectiveness.

Finally, FDA's decision was consistent with its actions regarding the products MiMedx cites as well as other products. FDA also reasonably classified Axiofill as a biological product because—as MiMedx does not dispute—Axiofill meets the biological product definition but not the device definition. MiMedx argues that FDA's decision here was inconsistent with the agency's actions in other cases, but it fails to show any inconsistency.

In sum, FDA reasonably determined that Axiofill is not a 361-only HCT/P but should instead be classified as a biological product. FDA correctly applied its regulations, and its decision was consistent with its actions in other cases. Thus, the Court should grant the government's cross-motion for summary judgment and deny MiMedx's motion for summary judgment.

BACKGROUND

I. Statutory and Regulatory Background

A. FDA's Regulation of Biological Products and Devices

FDA regulates biological products under the PHSA. A "biological product" is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). Companies must obtain FDA approval before marketing a biological product. *See id.* § 262(a)(1).

FDA regulates devices under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.* A "device" is defined as, among other things, an instrument "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease," which "does not achieve its primary intended purposes through chemical action within or on the body" and "which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 U.S.C. § 321(h)(1). Unless they fall within an exemption, medical devices must receive FDA marketing authorization before they may be marketed. *See id.* §§ 360(k), 360(l), 360(m), 360c(f)(1)–(2), 360e.

B. Human Cells, Tissues, or Cellular or Tissue-Based Products

HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer

into a human recipient." 21 C.F.R. § 1271.3(d). FDA has long recognized that different HCT/Ps may pose different levels of risk to health and safety. FDA accordingly developed a "tiered, risk-based approach to regulating HCT/P's" in which "the regulation of different types of human cells, tissues, and cellular and tissue-based products will be commensurate with the public health risks presented." 66 Fed. Reg. at 5447, 5449; *see* 42 U.S.C. § 264(a).[1] This framework is particularly aimed at "preventing unwitting use of contaminated tissues," "preventing improper handling or processing that might contaminate or damage tissues," and "ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed." FDA, *Proposed Approach to Regulation of Cellular and Tissue-Based Products* 6 (Feb. 28, 1997), https://perma.cc/M2QS-PPNC; *see* AR674.

In some cases, the risks associated with HCT/Ps are adequately addressed under Section 361 of the PHSA, which provides FDA with regulatory authority

[1] The regulatory text and purpose were established as part of a public rulemaking process involving many opportunities for stakeholder participation and comment on the provision and its rationale. This process began with the 1997 publication of FDA's "Proposed Approach" to the regulation of HCT/Ps, 62 Fed. Reg. 9721 (Mar. 4, 1997), and included public meetings and opportunities to comment on notices of proposed rulemaking. *See id.*; 63 Fed. Reg. 26744 (May 14, 1998); 64 Fed. Reg. 52696 (Sept. 30, 1999); 66 Fed. Reg. 1508 (Jan. 8, 2001); 66 Fed. Reg. 5447 (Jan. 19, 2001); 69 Fed. Reg. 29786 (May 25, 2004); 69 Fed. Reg. 68612 (Nov. 24, 2004).

to "prevent the introduction, transmission, or spread of communicable diseases." 42 U.S.C. § 264(a). HCT/Ps "regulat[ed] solely under section 361 of the PHS Act and 21 C.F.R. Part 1271," the implementing regulations, are subject, for example, to registration, manufacturing, and reporting requirements. AR674; *see* 21 C.F.R. § 1271.10(b). But they "do not require premarket approval." AR674. To qualify for this limited form of regulatory oversight, HCT/Ps must meet specified criteria. 21 C.F.R. § 1271.10(a). If any criterion is not met, and if certain exceptions inapplicable here do not apply, then "the HCT/P will be regulated as a drug, device, and/or biological product" and subject to applicable regulations, including Part 1271, as well as premarket review. AR674–75; *see* AR300.

FDA regulations establish four criteria that must be satisfied for an HCT/P to be "regulated solely under section 361" of the PHSA and 21 C.F.R. Part 1271. *See* 21 C.F.R. § 1271.10(a). Two of these criteria are relevant here.

First, the HCT/P must be "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). For "structural tissue" (which is the tissue type at issue here), minimal manipulation means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1).[2] FDA guidance

[2] Processing "includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization." AR679; *see* 21 C.F.R. § 1271.3(ff).

explains that the "[o]riginal relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions." AR678.[3] Such characteristics may include "strength, flexibility, cushioning, covering, compressibility, and response to friction and shear." AR681. The minimal manipulation criterion is an important part of FDA's risk-based framework: "[p]rocessing that alters the original characteristics of the HCT/P[] raises increased safety and effectiveness concerns for the HCT/P because there would be less basis on which to predict the product's function after transplantation." AR678; *see* 66 Fed. Reg. at 5457 (minimal manipulation criterion "serves as a valid indicator of those HCT/P's that present fewer risks and that are most appropriately regulated solely under section 361 of the PHS Act and part 1271").

Second, the HCT/P must be "intended for homologous use only." 21 C.F.R. § 1271.10(a)(2). "Homologous use" means "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P

[3] FDA issued the guidance pursuant to its good guidance practice regulations, 21 C.F.R. § 10.115, providing stakeholders the opportunity to offer comments and seek clarification. The public process included many steps: publication of a draft guidance addressing minimal manipulation in December 2014; reopening of the comment period in October 2015; a public hearing in September 2016; publication of a final guidance in November 2017 (followed by a correction in December 2017); and an unrelated update in July 2020. *See* 82 Fed. Reg. 54290 (Nov. 17, 2017); 85 Fed. Reg. 43989 (July 21, 2020).

that performs the same basic function or functions in the recipient as in the donor." 21 C.F.R. § 1271.3(c). The homologous use criterion "reflects the Agency's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a non-homologous use, because there is less basis on which to predict the product's behavior." AR675; *see* 66 Fed. Reg. at 5458.

To be regulated as a 361-only HCT/P, an HCT/P must meet all four of the criteria in section 1271.10(a). Failure to meet any of the criteria is disqualifying.

II. Factual Background

A. Axiofill

MiMedx's product Axiofill is a dry powder that consists of "decellularized particulate human placental connective tissue matrix (placental disc ECM)" derived from human placental disc. AR256. The Axiofill manufacturing process isolates the placental disc ECM by "remov[ing] cellular components and other non-intrinsic material, such as maternal blood, debris from other maternal tissues and/or from the child, and contaminating microorganisms." AR256–57. It does so by subjecting the placental disc to a series of processing steps that include chopping, rinsing with water and a chemical reagent, and straining. AR257 n.2. The resulting material "is then lyophilized [i.e., freeze dried], cut into 3x1x1 cm

pieces, ground by a centrifugal mill, and then passed through a 1 mm sieve into 40 mL glass vials." AR257 n.2.

Axiofill is intended to "replace or supplement damaged or inadequate integumental tissue," which "refers to the body's outermost layer and protective covering, in particular the skin." AR257.

B. MiMedx's Pre-Request for Designation and FDA's Response

There are two ways for a sponsor to receive an assessment from FDA's Office of Combination Products regarding whether a product is classified as a 361-only HCT/P or as a drug, device, or biological product. *See* AR695–96. The first option is to submit a Pre-Request for Designation (Pre-RFD) to "obtain preliminary feedback on the classification for [an] HCT/P." AR696. The second option is to submit a Request for Designation (RFD) to "obtain a formal Agency decision regarding the regulatory identity or classification of an HCT/P." *Id.*

On March 22, 2023, MiMedx submitted a Pre-RFD arguing that Axiofill qualifies as a 361-only HCT/P. AR16–18. On October 18, 2023, FDA responded to MiMedx's Pre-RFD. AR99–106. FDA's "preliminary assessment" was that Axiofill "appears to be an HCT/P that does not meet all the criteria" for a 361-only HCT/P. AR100. FDA preliminarily found that Axiofill does not meet the minimal manipulation criterion because "the processing [of Axiofill] alters the original relevant characteristics of the HCT/P relating to its utility for

reconstruction, repair, or replacement." AR102; *see* AR100–02. FDA found that Axiofill "appears to be a biological product" and "does not appear to meet the device definition" because it "achieves its primary intended purpose through chemical action within or on the body." AR104–05.

C. MiMedx's Request for Designation

On January 12, 2024, MiMedx submitted an RFD arguing that Axiofill meets the criteria for a 361-only HCT/P. AR241–55. Regarding minimal manipulation, MiMedx argued that Axiofill's "original relevant characteristics are its properties as a decellularized ECM that serves as a scaffold for cellular ingrowth" and that after processing, "the resulting particulate retains the ECM's capacity to allow cellular ingrowth." AR248; *see* AR248–50. This argument rested on two premises that FDA had rejected: First, that the appropriate "unit of analysis" in applying the minimal manipulation definition was "the *placental disc ECM*" (or Axiofill) rather than the "placental disc *as a whole*." AR249. Second, that the "functions the tissue performs in the donor" are irrelevant. AR249–50.

Regarding homologous use, MiMedx argued that "AXIOFILL performs the same basic function (providing a scaffold for cellular ingrowth) in the recipient as in the donor." AR250; *see* AR250–51. MiMedx also argued that Axiofill satisfied the remaining criteria in 21 C.F.R. § 1271.10(a). AR251.

Finally, MiMedx argued that the regulation of certain other products as 361-only HCT/Ps should guide Axiofill's classification. In particular, MiMedx pointed to Interfyl, which it asserted is the same as a product FDA considered in 2004 (the "2004 Product"), and demineralized bone matrix (DBM) powder. AR251–55.

D. FDA's Designation Letter

On March 22, 2024, FDA issued a Designation Letter in response to MiMedx's RFD. AR256–69. FDA determined that Axiofill is not a 361-only HCT/P, but instead should be regulated as a biological product. AR258.

FDA found that Axiofill is not minimally manipulated. AR258. FDA explained that it "considers the placental disc to be a structural tissue for the purpose of applying the HCT/P regulatory framework," and that "[f]or structural tissue, minimal manipulation means that the processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." AR258 (citing 21 C.F.R. § 1271.3(f)(1)). The agency further explained that the "[o]riginal relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions." *Id.*[4]

[4] FDA's explanation was consistent with the agency's guidance. AR678; AR681.

FDA clarified that here, the appropriate starting point for the minimal manipulation analysis "is the original relevant characteristics of the placental disc," which "is the HCT/P that exists in the donor" and "is the tissue from which [MiMedx] identif[ied] AXIOFILL as being processed."[5] AR261. Based on "[t]he relevant scientific literature," the agency considered whether the processing alters the original relevant structural characteristics of the placental disc related to its utility to act as a "selective barrier that provides a transport function." AR259 n.6. The agency explained that these original relevant characteristics include the placental disc's "cohesive physical three-dimensional structure" because that structure "is critical" to the placental disc's "ability to act as a selective barrier that provides a transport function." AR262; *see* AR284–85; AR321; AR749. FDA explained that this structure "is likely altered by [MiMedx's] processing," and thus "the processing alters the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement." AR262; *see* AR284–85; AR321; AR749.[6]

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[5] Although MiMedx's brief refers to Axiofill as consisting of ECM, *e.g.*, Dkt. No. 33 ("Mot.") at 1, its RFD makes clear that the source material for the product is placental disc. Indeed, the very first sentence of the RFD's Product Description section states that "AXIOFILL is made from human placental disc." AR241.

[6] For example, FDA pointed out that "the processing of [Axiofill] includes steps, such as milling, lyophilization, and decellularization, that likely contribute to disruption of some or many of the collagenous structures present in the native

FDA noted that MiMedx's "proposed approach – i.e., applying the minimal manipulation analysis to the processed HCT/P that is intended for implantation – would be contrary to the text and purpose of the regulation." AR259–60. Regarding the text, FDA explained that the plain language of the regulation refers to *original* relevant characteristics, i.e., the characteristics that allowed the tissue to achieve its role "at the point of the tissue's origin, which is in the donor." AR260. Regarding the purpose, FDA noted that it "would undermine the purpose of the minimal manipulation criterion" to start with "the ECM in [Axiofill] that does not exist in nature *absent* [MiMedx's] processing," since that approach would fail to account for certain effects of processing. *Id.*

FDA also rejected MiMedx's argument that Axiofill is comparable to other 361-only HCT/Ps. FDA stated, for example, that based on available information, the tissue sources for Interfyl and the 2004 Product are different from the tissue source for Axiofill, and they have different anatomy, histology, and physiology and perform different functions. AR263–65. For DBM powder, FDA noted that

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placental disc tissue." AR262. Because "these structures form the sites for the exchange of gases and metabolites between the maternal and fetal blood, their disruption would alter the original relevant structural characteristics of the placental disc relating to its utility to act as a selective barrier." *Id.* The processing of Axiofill is "also likely to contribute to the degradation of GAG chains from collagen and proteoglycans, which play functional, structural roles in the tissue, such as forming electrochemical barriers." *Id.*

bone and the placental disc have different original relevant characteristics, and that FDA's regulation of DBM powder was consistent in focusing on the original relevant characteristics of a tissue in the donor, not in the recipient. AR265–66.

FDA "note[d] that [Axiofill] also does not appear to meet other criteria in [21 C.F.R. §] 1271.10(a), including, for example, 1271.10(a)(2)" — the homologous use criterion. AR266 n.27. But FDA found that it was "not necessary to address" homologous use "because an HCT/P must meet all the criteria in 1271.10(a)" to qualify as a 361-only HCT/P, yet Axiofill failed at least the minimal manipulation criterion. AR267 n.27; *see* AR266.

FDA explained that "[a]n HCT/P that does not meet all of the criteria in 1271.10(a) is regulated as a drug, device, and/or biological product." AR266–67 (citing 21 C.F.R. § 1271.20). The agency noted that MiMedx's RFD did "not propose a classification for [Axiofill] beyond that of" a 361-only HCT/P. AR267. Nonetheless, FDA provided feedback regarding the appropriate product classification based on the information available to the agency. *Id.*

FDA found that Axiofill "is appropriately classified as a biological product" because it comprises, for example, "placental ECM proteins" and "other proteins" that "are intended to treat injured skin by replacing or supplementing missing or damaged ECM." AR267. FDA also found that Axiofill "does not meet the device definition" because it "achieves [its] primary intended

purpose"—"treatment of injured skin by replacement or supplementation of missing or damaged ECM"—"through chemical action within or on the body."[7] AR267–68. FDA explained, for example, that Axiofill "retains components with chemical actions (e.g., those that bind to bodily components, such as cells, to mediate bodily responses . . .) that can supplement damaged or inadequate ECM, through the wound healing process, in the context of injured skin." AR268. Thus, FDA concluded that Axiofill is "a biological product that does not meet the device definition." AR269.

LEGAL STANDARD

Under the APA, a court may set aside agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law." 5 U.S.C. § 706(2)(A). In deciding a motion for summary judgment in an APA case, the Rule 56 standard does not apply "because of the limited role of a court in reviewing the administrative record." *Lane v. United States*, 338 F. Supp. 3d 1324, 1331 (S.D. Ga. 2018). Rather, summary judgment in an APA case provides "the mechanism for deciding whether as a matter of law the agency action is supported by the administrative record and is otherwise consistent with the APA standard of review." *Id.*

[7] FDA clarified that this finding "assume[d] arguendo for purposes of this assessment that the primary intended purpose can be achieved by [Axiofill], which has not been demonstrated at this point." AR268 n.31.

The reviewing court may not "substitute its judgment for that of the agency," *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977), but must uphold the agency's action if it is "rational, based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *Motor Vehicle Mfrs. Ass'n, Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42–43 (1983). "A court simply ensures that the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021).

Where a party "claims the benefits of an exception" to a statutory rule, it bears the burden of establishing that the exception applies. *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314, 1322 (D.C. Cir. 2014) (quoting *United States v. First City Nat'l Bank of Houston*, 386 U.S. 361, 366 (1967)). Because MiMedx claims the benefit of having Axiofill regulated as a 361-only HCT/P under 21 C.F.R. § 1271.10(a), and because section "1271.10(a) is an exemption from the otherwise applicable provisions of the FDCA" and PHSA, MiMedx "bear[s] the burden of establishing" that the regulation applies to Axiofill. *Regenerative Sciences*, 741 F.3d at 1322.

ARGUMENT

I. FDA Reasonably Found that Axiofill Is More than Minimally Manipulated

There is no dispute that the definition of minimal manipulation for structural tissue applies here, and that this definition requires "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1); *see* AR258; Mot. 14–15. FDA reasonably found that Axiofill does not meet this requirement because the processing "alters" the original relevant characteristics of the placental disc relating to its role as "a selective barrier that provides a transport function."[8] AR259 & n.6; AR262; *see supra* pp. 12–15. MiMedx argues that FDA should have focused on Axiofill instead of the placental disc and should have focused on the function in the recipient rather than in the donor, and that FDA's decision was inconsistent with its decisions for other HCT/Ps. As discussed below, however, each of these arguments fails.

[8] Contrary to MiMedx's argument, FDA did not say that Axiofill must "retain the ability of *an intact placental disc* to provide a transportive barrier between 'fetal and maternal circulatory systems'" in order to satisfy the minimal manipulation requirement. Mot. 20–21 (citing AR259). Instead, FDA considered whether the Axiofill processing altered the placental disc's "cohesive physical three-dimensional structure," which was an "original relevant structural characteristic[] of [the placental disc] relating to its utility to act as a selective barrier that provides a transport function between different circulatory systems (e.g., the fetal and maternal circulatory systems)." AR259; AR262.

A. FDA Reasonably Applied the Minimal Manipulation Definition to the Placental Disc

MiMedx argues that the "minimal manipulation" definition applies to "the specific HCT/P that FDA is classifying for regulation" and "that is intended for implantation in the patient"—that is, Axiofill—and "not the larger tissue or organ from which it was derived"—that is, the placental disc. Mot. 17; *see id.* at 20 (arguing that the minimal manipulation definition should apply to "the ECM that comprises AXIOFILL"). But that argument contravenes the text and purpose of the regulation. Start with the text, which requires the HCT/P to be "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). The definition of minimal manipulation for structural tissues refers to the "original" relevant characteristics of the tissue. 21 C.F.R. § 1271.3(f)(1).[9] The plain language meaning of "original" is "of, relating to, or constituting an origin or beginning." Merriam-Webster Dictionary, "original," https://www.merriam-webster.com/dictionary/original; *see* AR260. Thus, FDA has explained that "original" relevant characteristics of tissue are characteristics "present in the tissue in the donor," AR681; *see* AR260; AR298. Here, the placental disc is present in the donor, but the particulate ECM preparation comprising Axiofill is not. Indeed, "particulate placental disc ECM

[9] MiMedx focuses on the term "[t]he HCT/P" in 21 C.F.R. § 1271.10(a)(1). Mot. 16–17. But it ignores that the "minimal manipulation" definition in 21 C.F.R. § 1271.3(f) specifies that its subject of analysis is the "tissues" or "cells," not the HCT/P potentially eligible for regulation as a 361-only HCT/P.

preparation is not an HCT/P that occurs in nature in the absence of processing." AR260. Thus, the "original relevant characteristics" must be characteristics of the placental disc, not characteristics of the post-processing particulate ECM preparation comprising Axiofill. *See* AR260; AR285–86; AR297–98; AR749.

The purpose of the minimal manipulation criterion also supports focusing on the placental disc rather than the processed HCT/P that is intended for implantation. FDA explained that this criterion is critical to the agency's "tiered, risk-based approach" because "HCT/Ps whose original relevant characteristics have been meaningfully altered present heightened risk and require greater regulation to ensure their safety and efficacy above and beyond the need, as with 361 HCT/Ps, to control the risk of communicable disease." AR260 (citation omitted); *see* AR678; 66 Fed. Reg. at 5457. This risk-based approach supports focusing the minimal manipulation analysis on the placental disc, which is the tissue that exists in nature and "is the tissue from which [MiMedx] identif[ied] AXIOFILL as being processed," AR261, because that would capture the full effect of the processing on the tissue. As FDA guidance explains, the minimal manipulation analysis should account for "all of the processing steps." AR679.

MiMedx's approach would undermine the purpose of the minimal manipulation criterion. As discussed above, particulate placental disc ECM preparation does not occur in nature absent processing. AR260. Thus, MiMedx's

approach of applying the minimal manipulation definition to that preparation would overlook the processing steps employed to create that preparation. These processing steps include cutting the isolated placental disc into 4x4x4 cm pieces, rinsing in water, chopping with a mechanical mixer, separating tissue from the liquid using a strainer, and rinsing several times with a reagent that includes a decellularization agent. AR245–47. In short, MiMedx's approach would not account for the full effect of "all of the processing steps," thus undermining FDA's "tiered, risk-based approach." AR260; AR678–79; *see* 66 Fed. Reg. at 5457.[10]

The focus on the tissue in the donor is also consistent with how FDA understands the antecedent question of whether the tissue is structural. *See* 21 C.F.R. § 1271.3(f). FDA guidance explains that "[t]o apply the minimal manipulation criterion, you first determine whether the HCT/P is structural or cellular/nonstructural" based on "the characteristics of the HCT/P in the donor, before recovery and before any processing that takes place." AR679. Just as the

[10] Even if it were appropriate to assess the effects of processing on the ECM and not the placental disc, MiMedx's RFD did not contain evidence "compar[ing] the organization of the ECM in the tissue before and after processing." AR263 n.20. The studies submitted did "not speak to whether the processing alters the specific composition or the structural organization of the placental disc ECM, which are critical to the placental disc's utility to act as a selective barrier that provides a transport function." *Id.*

focus is on the tissue in the donor in determining whether the "tissue" is structural, the focus continues to be on the tissue in the donor in determining whether the original relevant characteristics of the "tissue" have been altered. *See* 21 C.F.R. § 1271.3(f).

Finally, MiMedx cites *United States v. US Stem Cell Clinic, LLC*, 998 F.3d 1302 (11th Cir. 2021), in which the court applied the definition of homologous use to the processed HCT/P marketed by a clinic, not to the tissue from which that HCT/P was derived. *Id.* at 1311; Mot. 18–21.[11] But MiMedx's argument rests on a brief portion of the opinion concerning the homologous use criterion—not the minimal manipulation criterion, which was the basis for the Axiofill classification. *See* AR261 n.15; AR286; AR297–98.

The homologous use analysis in *US Stem Cell Clinic* should not be grafted onto the minimal manipulation analysis here, because those two criteria mitigate against different sources of risk. The homologous use criterion compares the HCT/P's intended function in the recipient to its function in the donor and asks whether the intended use is homologous. The rationale for this criterion is that HCT/Ps intended for a nonhomologous use in the recipient carry greater risk.

[11] Specifically, the court applied the homologous use definition to a stem cell product (referred to as "stromal-vascular fraction") derived from body fat ("adipose tissue"), rather than to the body fat itself. 998 F.3d at 1311.

See 21 C.F.R. § 1271.3(c); AR675; 66 Fed. Reg. at 5458. The minimal manipulation criterion, by contrast, is not concerned with the intended use in the recipient. Instead, it asks whether the processing alters "the original relevant characteristics of the tissue," 21 C.F.R. § 1271.3(f)(1), because such processing increases risk, *see* AR678; 66 Fed. Reg. at 5457. Thus, the minimal manipulation criterion is designed to account for the effects of processing, which the homologous use criterion is not. MiMedx cannot escape scrutiny of its processing steps under the minimal manipulation criterion by importing *US Stem Cell Clinic*'s analysis of the homologous use criterion.[12]

B. FDA Reasonably Focused on the Characteristics of the Placental Disc Related to the Placental Disc's Function in the Donor

MiMedx argues that "the minimal-manipulation requirement is met if the processing does not alter the original characteristics of the HCT/P that make it useful in the recipient," and faults FDA for "requir[ing] preservation of characteristics of the placental disc that relate to its utility *in the donor*." Mot. 22–23. But it was appropriate for FDA to consider the original characteristics of the

[12] MiMedx seeks to justify importing *US Stem Cell Clinic*'s homologous use analysis by noting that the criteria for a 361-only HCT/P require that "[t]he HCT/P" be both minimally manipulated and intended for homologous use. Mot. 19–20; 21 C.F.R. § 1271.10(a)(1)–(2). But as discussed above, this argument ignores the definitions of "minimal manipulation" and "homologous use," which specify the subject of analysis for those definitions, such as the "tissues" or "cells." 21 C.F.R. § 1271.3(c), (f); *see supra* n.9.

placental disc that are relevant to the function of the placental disc in the donor, because those characteristics "relat[e] to the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1).

"Utility" means "fitness for some purpose or worth to some end." Merriam-Webster Dictionary, "utility," https://www.merriam-webster.com/dictionary/utility. Thus, the "original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement," 21 C.F.R. § 1271.3(f)(1), means the original characteristics of the tissue that give the tissue the property of being fit, or useful, to provide reconstruction, repair, or replacement. *See* AR259; AR681.

The tissue's function in the donor indicates how the tissue could be fit, or useful, to provide reconstruction, repair, or replacement. Thus, FDA has explained that "[t]he structural tissue's utility for reconstruction, repair, or replacement relates to how that tissue functions in the donor." AR259; AR681. And the "[o]riginal relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions." AR259; AR681; *see* AR681–85.[13]

[13] Here, FDA explained that the original relevant characteristics of the placental disc relate to the placental disc's utility to serve as a selective barrier, and that MiMedx's processing disrupts the physical structure of the placental disc, which is critical to the placental disc's ability to act as a selective barrier. AR259 n.6;

MiMedx argues that original relevant characteristics are "the original characteristics of the HCT/P that make it useful in the recipient"—that give it "utility for reconstruction, repair, or replacement in the recipient." Mot. 22–23. But the minimal manipulation criterion does not "assess the actual utility, i.e., effectiveness, of the tissue in the recipient." AR261 n.14. It is "not designed to establish an effectiveness standard for HCT/Ps." *Id.* Instead, the minimal manipulation criterion and the other criteria in section 1271.10(a) are designed to identify HCT/Ps whose risks are adequately addressed under limited regulatory oversight and *without* premarket review for safety and effectiveness. *See id.*; AR300; AR674–75. Thus, FDA properly does not ask which characteristics make the HCT/P "useful in the recipient," Mot. 22–23, but instead asks which

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AR262. Such altering of the physical integrity of the placental disc, FDA explained, alters the tissue's original relevant characteristics relating to its utility for reconstruction, repair, or replacement. AR262. When the structural placental disc tissue is processed so that it no longer has the physical integrity of a structural tissue, it no longer has utility for reconstruction, repair, or replacement. *Id.* This analysis is consistent with FDA's guidance. *See, e.g.*, AR682 (Example 10-2-b, explaining that the "[o]riginal relevant characteristics of amniotic membrane relating to its utility to serve as a barrier generally include the tissue's physical integrity, tensile strength, and elasticity," and that these original relevant characteristics are altered when "[a] manufacturer grinds and lyophilizes amniotic membrane and packages it as particles").

"properties of th[e] tissue in the donor . . . contribute to the tissue's function or functions" in the donor, AR259; AR681.[14]

C. FDA's Decision Was Consistent with Its Treatment of Other Products

MiMedx argues that FDA's decision was inconsistent with its actions regarding the 2004 Product and DBM powder. Mot. 25–29. But FDA's decision here was consistent with its actions in those and other cases.

The 2004 Product. MiMedx argues that the 2004 Product is "essentially identical" to Axiofill. Mot. 25. But FDA explained that the 2004 Product[15] and Axiofill are derived from different tissue sources, which have different anatomy, histology, and physiology and perform different functions. AR263–65; *see* AR286; AR298. For example, FDA explained that the tissue source for the 2004 Product "appears to be the chorionic plate of human placentas." AR263. By contrast, "the isolated tissue source for [Axiofill] is the placental disc, which, although it

[14] Contrary to MiMedx's argument, FDA has not "routinely" looked to an HCT/P's "intended use in patients" for purposes of minimal manipulation. Mot. 24 n.8. The 2005 RFD response that MiMedx cites applied the minimal manipulation definition for cells and nonstructural tissues, 21 C.F.R. § 1271.3(f)(2); AR348, which differs from the definition for structural tissues (applicable here), 21 C.F.R. § 1271.3(f)(1), and addresses "different safety and efficacy concerns," AR678. By contrast, FDA's "routine" application of the minimal manipulation criterion for structural tissues is set out in the agency's guidance, AR669–96, which is consistent with FDA's decision here.

[15] FDA's explanation also related to Interfyl, which MiMedx asserted was the same as the 2004 Product. AR263–65.

contains the chorionic plate, has significantly different anatomy, histology, and physiology than the chorionic plate on its own." AR263–64. In particular, "unlike the chorionic plate of the placenta, the placental disc is a highly vascularized tissue containing distinctive structures such as the basal plate, the placental villi, and cotyledons that are not present in the chorionic plate." AR264. FDA further explained that "the placental disc does not serve a connective tissue function like the chorion," but instead "is a selective structural barrier that provides a transport function between fetal and maternal circulations." *Id.*

As discussed above, the original relevant characteristics of a tissue "generally include the properties of that tissue in the donor that contribute to the tissue's function or functions." AR678. The 2004 Product and Axiofill are derived from different tissue sources with different functions. Thus, the minimal manipulation analyses for the two products are different, and FDA's determination that the 2004 Product is minimally manipulated is not determinative for Axiofill.[16]

MiMedx responds that "the function of the ECM will be the same" in all parts of the placenta—to provide "physical scaffolding for the cellular constituents." Mot. 26. But as discussed above, the starting point for the minimal

[16] This is true even if the processing of the 2004 Product and Axiofill is the same. However, MiMedx has not produced evidence that the processing is the same.

manipulation analysis here is not the ECM, but rather the placental disc, which is the tissue from which Axiofill is processed. *See supra* pp. 19–23. Because the 2004 Product and Axiofill have different tissue sources with "significantly different anatomy, histology, and physiology" and different functions, AR263–64, the analysis regarding whether the processing alters the original relevant characteristics differs, too.

Finally, MiMedx argues that FDA's analysis of the 2004 Product "focused on *the ECM*, not the entire chorionic plate." Mot. 27. But MiMedx does not, and cannot, provide any record support for that assertion. MiMedx simply asserts that "FDA did not conclude (nor could it have) that the ECM in the 2004 [P]roduct retained all the properties of the chorionic plate *as a whole*." Mot. 27. However, the minimal manipulation requirement does not require the processed HCT/P to retain *all* the properties of the tissue in the donor. Instead, the processing of the HCT/P must not alter *the original relevant characteristics* of the tissue relating to that tissue's function in the donor. In the case of Axiofill, FDA found that the product was more than minimally manipulated because the processing altered the placental disc's "cohesive physical three-dimensional structure," which "is critical" to the placental disc's "ability to act as a selective barrier that provides a transport function." AR262; *see* AR 258. There is no inconsistency between FDA's decisions for Axiofill and for the 2004 Product.

Demineralized Bone Matrix Powder. MiMedx argues that FDA's Axiofill decision is inconsistent with its "position that demineralized bone matrix powder *is* minimally manipulated." Mot. 27. But FDA applied the same approach in both cases: it considered whether the processing alters the original relevant characteristics of the tissue, which "generally include the properties of that tissue in the donor that contribute to the tissue's function or functions." AR678. FDA found that the Axiofill processing alters the placental disc's original relevant characteristics relating to that tissue's function in the donor, specifically the placental disc's "cohesive physical three-dimensional structure." AR258; AR262. In FDA's guidance, cited in its Designation Letter, AR265–66, the agency applied the same approach in finding that DBM powder generally is minimally manipulated: it explained that "grind[ing] bone to form bone chips and particles" generally does "not alter the bone's original relevant characteristics relating to its utility to support bodily structures," which "include strength, and resistance to compression." AR681; *see* AR266.[17]

Contrary to MiMedx's argument, FDA did not require Axiofill to retain "all the characteristics" of the placental disc, just as it did not require DBM

[17] Contrary to MiMedx's assertion, FDA's evaluation of DBM powder did not "focus on the specific HCT/P intended for implantation rather than the larger tissue or organ from which that HCT/P is extracted." Mot. 29.

powder to "retain all the characteristics of intact bones." Mot. 28. Instead, FDA considered whether the processing of Axiofill altered the original relevant characteristics of the placental disc, including its "cohesive physical three-dimensional structure," AR262, just as it considered whether the processing of DBM powder altered the original relevant characteristics of bone, "includ[ing] strength, and resistance to compression," AR681; *see* AR266.

Other Products. FDA's approach here is also consistent with its evaluation of other products. For example, [redacted]

FDA also found that the HCT/P in RFD120042 was "more than minimal[ly] manipulat[ed]." AR358. The tissue source was "the entire placenta," which FDA explained has "significantly different anatomy, histology, and

physiology than the chorion" from which the 2004 Product was manufactured. AR357. FDA explained that the processing "destroyed" the original relevant characteristics of the whole placenta, and thus the HCT/P was more than minimally manipulated. *Id.* These examples are consistent with FDA's Axiofill analysis because FDA asked whether the processing altered the original relevant characteristics of the tissue from which the HCT/P was manufactured, and observed that the minimal manipulation question was different for the 2004 Product because that product was manufactured from the chorion.

II. FDA's Decision Did Not Rely on the Homologous Use Criterion

MiMedx argues that Axiofill satisfies the homologous use criterion. Mot. 29–32. But FDA declined to decide that issue "because an HCT/P must meet all the criteria in 1271.10(a)" to be regulated as a 361-only HCT/P, yet Axiofill failed at least the minimal manipulation criterion. AR267 n.27. Thus, FDA's classification of Axiofill did not rest on any finding regarding homologous use.

III. FDA Reasonably Classified Axiofill as a Biological Product

After finding that Axiofill "is not eligible for regulation solely under section 361 of the PHS Act and the regulations in 21 C.F.R. Part 1271," FDA explained that it is properly "regulated as a drug, device, and/or biological product." AR266–67 (citing 21 C.F.R. § 1271.20). FDA found that Axiofill "is appropriately classified as a biological product" because it comprises, for

example, "placental ECM proteins" and "other proteins" that "are intended to treat injured skin by replacing or supplementing missing or damaged ECM." AR267. FDA also found that Axiofill "does not meet the device definition" because it "achieves [its] primary intended purpose"—"treatment of injured skin by replacement or supplementation of missing or damaged ECM"—"through chemical action within or on the body." AR267–68; *see* AR 326–27; 21 U.S.C. § 321(h)(1). These "scientific judgment[s] within [FDA's] area of expertise" merit a "high level of deference." *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) (quotations omitted); *see Balt. Gas & Elec. Co. v. Nat. Res. Def. Council, Inc.*, 462 U.S. 87, 103 (1983) (where an agency has made a "scientific determination" that is "within its area of special expertise," "a reviewing court must generally be at its most deferential"); *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 108 F.4th 836, 840 (D.C. Cir. 2024) ("In analyzing the FDA's decision, we must be careful not to unduly second-guess an agency's scientific judgments, and will affirm the FDA's decision so long as it is reasonable and reasonably explained." (quotations omitted)).

MiMedx does not dispute FDA's explanation for why Axiofill "is appropriately classified as a biological product" and "does not meet the device definition." AR267–68. Instead, MiMedx argues only that FDA's classification of Axiofill as a biological product is inconsistent with the agency's classification of

other products as devices. Mot. 32–35. But MiMedx fails to show any inconsistency.

Although MiMedx cites examples of products that FDA regulates as devices, none of those examples involved products with the same primary intended purpose as Axiofill.[18] *See* AR267–68. MiMedx cites products reviewed by FDA that were intended for the "management of wounds." Dkt. No. 1-16 at 5[19]; *see* FDA, 510(k) Clearance for InnovaMatrix PD, No. K211902 (Sept. 28, 2022), *available at* https://www.accessdata.fda.gov/cdrh_docs/pdf21/K211902.pdf; 21 U.S.C. §§ 360(k), 360c(f), (i).[20] It also cites the "Corplex P" product, which is intended to "cover, protect, and provide a moist wound environment." Dkt. No. 1-20 at 5.[21] Axiofill, by contrast, has a different "primary intended purpose": the "treatment of injured skin by replacement or supplementation of missing or damaged ECM." AR267. Because the definition of "device" requires that a product "does not achieve its primary intended purposes through chemical

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[18] In addition to a product's primary intended purpose, other considerations can also inform a product's classification.

[19] The page numbers cited for Dkt. No. 1-16 and Dkt. No. 1-20 (cited below) are the page numbers generated by CM/ECF.

[20] MiMedx also cites statements in an FDA consultation memorandum, Mot. 34 (citing AR326 n.27), but these statements do not show that FDA found any comparable product met the device definition.

[21] MiMedx does not analyze whether Corplex P has the same composition and manufacturing process as Axiofill.

action within or on the body," 21 U.S.C. § 321(h)(1), and Axiofill has a different primary intended purpose than the products MiMedx cites, the classification analysis for Axiofill was different. There was no inconsistency between FDA's classification of Axiofill as a biological product and its regulation of the other products as devices.

In evaluating MiMedx's RFD, FDA similarly explained that other products regulated as devices differ from Axiofill in their primary intended purposes. For example, a consultation memorandum explained that "most wound dressings" regulated as devices are intended for "wound management and are understood to achieve their primary intended purpose by physically covering the wound to protect it and/or to maintain a moist wound environment." AR326 n.27.[22] The agency also explained that, while there are "interactive wound and burn dressings where scaffolding claims are publicly made" that are regulated as devices, these products' "mechanism [of action] is understood to be physical/passive," and they have "different processing, different final composition, and different intended use/claims" than Axiofill. *Id.* For Axiofill,

[22] MiMedx tries to dismiss this analysis by arguing that it was not repeated in FDA's Designation Letter. Mot. 34. But in evaluating an APA claim, the question is whether the agency's decision was reasonable based on "the whole record or those parts of it cited by a party." 5 U.S.C. § 706; *see Prometheus Radio Project*, 141 S. Ct. at 1158; *Camp v. Pitts,* 411 U.S. 138, 142 (1973); *Hill Dermaceuticals, Inc. v. FDA*, 709 F.3d 44, 47 (D.C. Cir. 2013).

FDA explained that MiMedx "provided no testing to support [its] assertions that [Axiofill] achieves its primary intended purpose as a dermal ECM supplement physically," but that "open scientific literature discusses the importance of numerous molecules known to be in AXIOFILL, and known to be in placental derived ECM generally, that have direct biochemical roles that are required to achieve the primary intended purpose of this product." AR326–27; *see* AR267–69.

Finally, MiMedx argues that the products it cites are comparable to Axiofill because they are "ECM products." Mot. 33. But even if products have the same components, they do not necessarily have the same classification. As discussed above, the relevant question in determining whether a product meets the device definition is whether it "achieve[s] its primary intended purposes through chemical action within or on the body." 21 U.S.C. § 321(h)(1). Because Axiofill and the products MiMedx cites have different primary intended purposes, the classification analyses are different.

CONCLUSION

The Court should grant the government's cross-motion for summary judgment and deny MiMedx's motion for summary judgment.

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Respectfully submitted,

/s/ Noah T. Katzen
NOAH T. KATZEN
D.C. Bar No. 1006053
Trial Attorney
Consumer Protection Branch
Civil Division
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044-0386
(202) 305-2428
(202) 514-8742 (fax)
Noah.T.Katzen@usdoj.gov

Counsel for Defendants

CERTIFICATE OF COMPLIANCE

I hereby certify, pursuant to Local Rules 5.1 and 7.1(D), that the foregoing brief has been prepared using Book Antiqua, 13-point font.

September 12, 2024

/s/ Noah T. Katzen
Noah T. Katzen

CERTIFICATE OF SERVICE

I hereby certify that this document, filed through the CM/ECF system, will be sent via electronic mail to the registered participants as identified on the Notice of Electronic Filing.

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/s/ Noah T. Katzen
Noah T. Katzen